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Potential Role of Periodontopathogens in Rheumatoid Arthritis

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Abstract

Periodontal disease, particularly the chronic form of periodontitis, is a widespread inflammatory condition caused by pathogenic bacteria, such as *Porphyromonas gingivalis*. This review explores the potential role of periodontopathogens, particularly *Porphyromonas gingivalis*, in the development and progression of rheumatoid arthritis. Rheumatoid arthritis is a systemic autoimmune disorder characterized by joint inflammation and damage. Both periodontitis and rheumatoid arthritis share common inflammatory mechanisms, driven by proinflammatory cytokines and immune dysregulation. *Porphyromonas gingivalis*, via its pathogenic determinants, that is, gingipains and peptidyl arginine deiminase, facilitates the citrullination of proteins, leading to the generation of anti-citrullinated protein antibodies, a key feature in rheumatoid arthritis pathogenesis. The reciprocal relationship between periodontitis and rheumatoid arthritis is further supported through evidence showing that individuals with periodontitis are at a higher risk for rheumatoid arthritis, and vice versa. Both circumstances exhibit similar inflammatory pathways, involving cytokines like tumor necrosis factor alpha, interleukin 1 and interleukin 6 and tissue degradation mediated by matrix metalloproteinases.

Keywords: *Rheumatoid arthritis, Periodontitis, Porphyromonas gingivalis*

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Introduction

Periodontal disease, encompassing gingivitis and periodontitis (PD), is defined by the inflammation of the gums and other structures, frequently resulting from the buildup of detrimental bacteria in the oral cavity. Specific periodontopathogens, particularly *Porphyromonas gingivalis* (*P. gingivalis*), have been associated with the onset and aggravation of systemic inflammation [1]. Rheumatoid arthritis (RA) is a tenacious, systemic inflammatory condition that principally impacts the joints, culminating in pain, rigidity, and possible joint abnormalities. Precise RA etiology is unclear; nonetheless, it is recognized to engage a confluence of genetic, environmental, and immune-mediated variables [2]. Research indicates that periodontopathogens may have a role in RA by generating autoantibodies, such as anti-citrullinated protein antibodies (ACPA), which activate immune responses that exacerbate joint inflammation. The bidirectional link between periodontal disease and RA, where in one condition may affect the onset or advancement of the other, has generated significant scholarly interest [3,4].

This review aims to examine the potential link between periodontal infections and RA, focusing on how periodontopathogens, especially *P. gingivalis*, may contribute to the initiation of immune responses that facilitate the onset and advancement of RA.

Materials and Methods

For this review, the authors executed an electronic search across many pertinent scientific databases, including SCOPUS, Google Scholar, PubMed, MDPI, and ResearchGate. The preliminary evaluation encompassed 130 publications

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published from 2020 to 2024 that featured the keywords "periodontitis," "Rheumatoid arthritis," and "*Porphyromonas gingivalis*."

Inclusion criteria

This study included recent papers, reviews, and case-control studies; all articles included in this review were published in English.

Exclusion criteria

Articles and research published prior to 2020 were omitted, as illustrated in Figure 1.

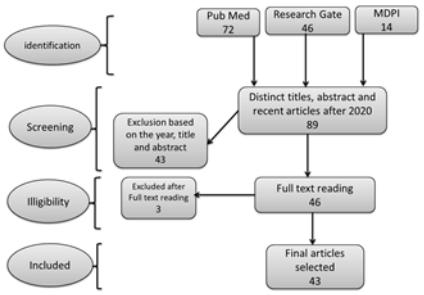

Figure 1. Progression of the search and selection procedure.

Periodontitis

Periodontitis is a persistent, damaging, and permanent inflammatory condition. It is the predominant cause of osteopenia and an infectious inflammatory ailment affecting humanity [5]. The World Health Organization classifies PD as unprecedented global event, exhibiting concerning frequency among various age demographics and geographic areas. It impact around 19% of the world's residents, representing more than a billion instances. The data concerning European nations reveals that over 50% of the population may experience some variant of PD, with over 10% afflicted by its severe manifestation. Incidence increases up to 70–85% among individuals of 60–65 years old [6]. From 1990 to 2019, PD prevalence rate rose globally by 8.44% [7,8]. The worldwide load of PD is considerable and has markedly escalated throughout the last three decades, posing a huge public health concern and necessitating the pursuit of novel therapeutic interventions [6].

Pathogenesis of Periodontitis

The pathogenesis of periodontal disease is defined by the interplay between bacterial plaque accumulation and inflammatory responses in the gingiva [9]. This connection activates fundamental molecular routes which ultimately result in the activation of host-derived proteases. This leads to periodontal ligaments marginal fibers degradation, junctional epithelium displacement, and subsequent bacterial biofilm proliferation along the root surface apically [10,11]. The microbiology of PD is intricate, primarily characterized by a transition in the microbial population from a largely Gram-positive, aerobic, health-associated biofilm to a predominance of Gram-negative anaerobes. Fundamental molecular investigations have found complexes of various bacterial species linked to severe chronic periodontitis, specifically *P. gingivalis*, *Tanerella forsythia*, and *Treponema denticola* [12]. A recent study shown that microbial populations associated with various periodontal conditions altered in an asynchronous manner during the reconstruction of biofilms following its initial elimination using supragingival cleaning. Research indicates that bacteria like *Abiotrophia spp.* and *Capnocytophaga spp.* may significantly influence the formation of plaque biofilms [13]. While this development seems to have a robust immunological-inflammatory foundation, both innate (sex and genetic variables) and obtained (obesity, stress, smoking, concurrent systemic disorders) risk determinants significantly contribute [14]. Soft and hard tissues around the teeth experience escalating damage from advancing inflammation due

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to both the direct, deleterious health risks associated with bacterial virulence factors found in dental plaque and the indirect consequences of the body's heightened, generalized inflammatory reaction to periodontopathogens [15]. Inflammation initiates a complicated interaction of proinflammatory cytokines, nitric oxide, matrix metalloproteinases (MMPs), prostaglandin E2, and various alternative inflammatory mediators. Elevated levels of tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, IL-11, and IL-17 facilitate the formation of osteoclasts through boosting nuclear factor kappa-β ligand receptor activator expression (RANKL) and diminishing osteoprotegerin production [11]. Moreover, active periodontal lesions demonstrate an overproduction of IL-17 and RANKL, alongside reduced concentrations of anti-inflammatory cytokines such as IL-10 and transforming growth factor beta1 (TGF-β1), indicating an aberrant immunological reaction. This disruption in the metabolism of bone not solely incline patients to periodontal disease but also suggests it in the capacity of possible risk determinant for conditions like rheumatoid arthritis, however, agreement is still hard to grasp [11,16].

The Keystone Periodontal Pathogen (*Porphyromonas gingivalis*)

The rod-shaped, Gram-negative, anaerobic bacteria known as *P. gingivalis* was identified in 85.75% of subgingival plaque in individuals with persistent periodontal disease [17]. The virulence components of *P. gingivalis* include fimbriae, haemolysin, hemagglutinins, a capsule, outer membrane vesicles, lipopolysaccharides, and gingipains [18]. The prevalence of *P. gingivalis* correlates with the severity of periodontal disease and has been recognized by researchers as a primary causal element in the PD progression. The keystone pathogen idea suggests that *P. gingivalis*, even in minimal quantities, might trigger chronic periodontal disease by altering the commensal bacterial community, resulting in dysbiosis and subsequent disease [19].

Role of *Porphyromonas gingivalis* in Periodontal Disease

In vivo investigations in mice have demonstrated that contagion with *P. gingivalis* induces osteoclastic activity [20]. *P. gingivalis* attaches to and infiltrates the epithelial layers, proliferates and induces periodontal disease. Although the epithelium serves as the primary obstacle in opposition to numerous diseases, including periodontal microbiome, *P. gingivalis* infiltrates gingival epithelium along with the fundamental connective tissues [23,24]. It plays a substantial role in the etiology of aggressive PD by eliciting elevated degrees of pro-inflammatory cytokines [25]. Serotypes K1 and K2 are linked to elevated expression of receptor activator RANKL. This element influences the generation and development of osteoclasts and triggers a robust T helper1 (Th1) and Th17 inflammatory reaction, leading to increased breakdown of alveolar osseous tissues and enhanced destruction of periodontal tissue [26]. The complement system safeguards the host against microbial infections via opsonization, chemotaxis, and infected cells destruction [22]. *P. gingivalis* exhibits resistance to the complement system via the activity of its enzymes or by surface chemicals that enable adaptation to the regulatory proteins of the host's complement. *P. gingivalis* inhibits the cascade process of complement component 5 convertase production within the complement system [22,27].

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Moreover, complement component 3 interacts with *P. gingivalis* fimbriae, facilitating the internalization of the bacteria by macrophages. *P. gingivalis* utilizes the synergy and crosstalk between complement and toll-like receptors to alter host defenses and evade elimination by the host [19]. Levels of complements proteins in crevicular fluid are diminished in individuals with periodontal disease [22,26]. *P. gingivalis* can evade neutrophils devastation through diminishing their antibacterial and chemotaxis efficacy [21,25]. The survival mechanisms of *P. gingivalis* lead to a remodeled microbiota, resulting in a dysbiotic condition that induces inflammatory diseases such as periodontal disease [19].

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune, systemic inflammatory disorder that impacts roughly 1% of the population. It is marked by persistent joint inflammation, destruction of bone and cartilage, and systemic extra-articular manifestations not directly associated with the musculoskeletal system [27], which occur in a significant proportion of patients, resulting in poorer disease outcomes [28]. RA patients frequently display diverse oral manifestations, notably the recognized association with Sjogren's syndrome, resulting in symptoms such as xerostomia. Additional oral concerns encompass temporomandibular joint abnormalities, methotrexate-induced ulcers, and an increasing emphasis on periodontal disease [29].

Pathogenesis of Rheumatoid Arthritis

Vulnerability and initiation of RA rise from ambient and hereditary variables. The most often used autoantibodies in clinical practice are ACPAs, which may be detected in RA patients years prior to symptom manifestation. Peptidyl arginine deiminase (PADI) facilitates the post-translational modification that transforms arginine or glycine residues in normal proteins into citrulline, a significant factor contributing to the abrogation of immunological tolerance in RA patients [30].
Non-resolving inflammation driven by aberrantly activated immune cells plays a crucial role in the development of RA. Immune cells penetrate the synovium diffusely; however, in some instances, T cells and B cells form consolidates, with or without follicular dendritic cells, leading to the formation of lymphoid consolidates or ectopic germinal centers [31]. This process contributes to the breakdown of self-tolerance and accelerates the pathogenesis of RA. In RA, the majority of proinflammatory cytokines originate from macrophages and fibroblast-like synoviocytes, including IL-1, IL-6 and TNF-α. TNF-α, a key proinflammatory cytokine in RA, enhances inflammation by activating the NF-κB pathway, which promotes osteoclast formation [31,32]. IL-1 similarly causes fast and powerful inflammatory reactions, primarily generated by macrophages in RA. IL-1 may additionally enhance IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, collagenase, and prostaglandins synthesis [31]. Large quantities of IL-6 in the synovial fluid of RA individuals may additionally transmit stimuli of pathogenic inflammation in RA- fibroblast-like synoviocytes via the Janus kinase pathway [33].

The association between rheumatoid arthritis and periodontitis

The findings from previous study have garnered significant interest from both Chinese and foreign scholars regarding the correlation between PD and RA. Cantley et al discovered that animals afflicted with both PD and

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RA exhibit more severe RA activity and an earlier commencement [34]. IL-1 and TNF-α are proinflammatory cytokines which significantly contribute to the pathogenesis of periodontal disease and RA. They prompt inflammatory cells to infiltrate the diseased area, resulting in bone degradation through the inflammatory mediators secretion and cytokines activation, which facilitates the breakdown of alveolar osseous tissue and collagen fibers degradation in periodontal disease [35]. Recent data demonstrates a substantial association between susceptibility to RA and the human leukocyte antigen DRB1 (HLA-DRB1) genetic locus, due to the binding of citrullinated self-peptides to HLA-DR molecules. *P. gingivalis*, a principal microbiome in periodontal disease and the only recognized human microbiome that expresses PADI, is pivotal. This enzyme generates citrullinated epitopes, which are recognized by ACPA in RA [36]. A prospective study revealed that persons with RA exhibited a greater prevalence of periodontal disease PD, especially in the midst of the individuals with increased concentrations of *P. gingivalis* in profound periodontal pockets, in comparison to healthy individuals [37]. The immunological processes resulting in advancing connective tissue breakdown and osseous tissue resorption, typical of RA, are also common in periodontal disease. Periodontal disease, a contagious ailment predominantly induced by bacterial species such as *P. gingivalis*, *Aggregatibacter actinomycetemcomitans, Tannerella forsythia*, and *Treponema denticola*, elicits both localized and systemic immunological reactions. Furthermore, the presence of oral bacterial DNA and antibodies in the synovial fluid and blood of patients with RA connect PD with the development of RA [11, 16]. A potential correlation between PD and RA may extend beyond causative relationships, presumably attributable to prevalent genetic and environmental risk determinants, including major histocompatibility class II HLA-DRB1 allele expression and tobacco use [11,38]. Although the underlying causes differ, numerous clinical and public health researchers suggest a link between RA and PD. Individuals with PD have an increased susceptibility to RA and vice versa; the frequency of PD is twice as high in RA individuals in comparison to the populace [11,37]. Furthermore, RA individuals with PD typically exhibit a more serious clinical progression, irrespective of gender, age, smoking or ethnicity status, in comparison to individuals without RA. Moreover, the two illnesses exhibit analogous pathways of tissue damage driven by inflammatory cells and proinflammatory cytokines, indicating that periodontal disease can contribute to the onset and continuation of autoimmune inflammatory responses observed in RA [11,39].

Role of *Porphyromonas gingivalis* in the Development of Rheumatoid Arthritis

The successful application of antibiotics for anaerobic microbial infections in RA suggests that bacteria may contribute to the formation of RA. Identification of bacterial DNA from anaerobes and elevated antibody titers opposed to it in the synovial fluid and serum of RA individuals at different disease phases supports the hypothesis that oral infections contribute to the etiology of RA [11,40].

Periodontal pathogens such as *P. gingivalis* can undermine the integrity of epithelial tissue, infiltrate human endothelial cells, and affect transcription and protein synthesis, thereby facilitating direct systemic entry into bloodstream. *P. gingivalis* can infiltrate primary human

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chondrocytes derived from patellar joints, leading to prolonged cell cycle advancement and heightened programmed cell death [11]. *P. gingivalis* synthesizes cysteine endopeptidase enzymes which are essential for bacterial homeostasis and infection mechanisms, including amino acids isolation from host and the formation of fimbriae [11,25]. *P. gingivalis* gingipains facilitate proteolytic enzymes activation including MMP-1, MMP-3, and MMP-9, along with the degradation of extracellular matrix host proteins such as collagen, fibronectin, and laminin. Additionally, gingipains induce the degradation of complement factors and enhance the permeability of blood vessels [11,41]. The pathogenesis of RA is associated with the involvement of *P. gingivalis* in the process of citrullination. Proteins experience a post-translational modification known as citrullination, converting arginine residues into citrulline [8,42]. The bacterium produces enzymes, including PADI, catalyze citrullination. The infection elicits immunological reaction which can lead to systemic consequences. Citrullination is a pivotal process in the pathogenesis of RA, as it generates antibodies against citrullinated proteins [8,43]. The citrullination mediated by *P. gingivalis* may facilitate the production of ACPAs, establishing a connection between periodontal disease and the onset or worsening of RA. Citrullinated proteins are commonly present in the synovial fluids of people with RA. The existence of *P. gingivalis* and its citrullination role inside of the mouth may affect the systemic dissemination of citrullinated peptides, intensifying synovial inflammation in predisposed people [36,43].

Conclusion

The growing body of evidence linking periodontitis, particularly the role of *P. gingivalis*, to the development and exacerbation of RA highlights the complex interactions between oral and systemic health. Periodontitis, a chronic inflammatory disease, is associated with a range of systemic conditions, with RA being one of the most compelling examples of such connections. The key periodontal pathogen *P. gingivalis* plays a central role in this relationship, not only by inducing local inflammation and bone resorption in the oral cavity but also by influencing systemic immune responses through mechanisms such as citrullination. *P. gingivalis* secretes PADI, an enzyme that catalyzes the conversion of arginine to citrulline, a critical process that generates autoantibodies against citrullinated proteins, a hallmark of RA. This molecular interaction suggests that oral bacteria may directly contribute to the immune dysregulation observed in RA, leading to the production of ACPA and the subsequent development of chronic joint inflammation. Additionally, the shared inflammatory mediators and cytokine profiles between PD and RA further reinforce the potential for a bidirectional relationship, where one condition may influence the progression of the other.

Given the significant prevalence of periodontitis worldwide, and the established connection between periodontal disease and RA, there is a pressing need for further research into the underlying mechanisms of this association. Understanding how *P. gingivalis* and other periodontal pathogens contribute to RA may offer new avenues for preventive and therapeutic strategies, not only targeting oral health but also the systemic inflammatory pathways involved in autoimmune diseases like RA. Integrating periodontal care into the management of RA could potentially improve patient outcomes and reduce disease severity, highlighting the importance of early detection and

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comprehensive treatment strategies that address both oral and systemic health.

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Conflict of Interest

The authors declare no conflict of interest.

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